REMARKS/ARGUMENTS

Claims 1 through 42 have been examined. The Examiner has acknowledged Applicants election with traverse of Group VI, claims 26 - 29, 32-34, and linking claims 25 and 31. The restriction has been reconsidered and made final by the Examiner. As such, claims 1-24, 30 and 35-42 have been withdrawn by the Examiner and claims 24-29 and 31-34 have been examined.

By this amendment Applicants have cancelled Claims 1-24, 30 and 35-42 as being directed to a non-elected invention without prejudice to prosecuting the subject matter of the cancelled claims in a related co-pending application. Claims 25 and 31 have been amended. In addition, claims 27-29, 33 and 34 have been cancelled without prejudice to further prosecution of the subject matter encompassed by the claims in a co-pending related application. No new matter has been added by any of the above amendments.

The Examiner has objected to the abstract and title alleging that they do not adequately describe the claimed inventions. Amendment of the abstract and title commensurate in scope with the invention of the instant claims has been required. As requested the title and abstract have been amended to be limited to antagonists of Rheb activity and their use in screening for compounds that can be used as a lead compound in the preparation of agents that can be used to treat growth related diseases. The amended title and abstract are believed to conform with the scope of the claims currently pending in the instant application.

Rejections Under 35 U.S.C. § 112:

Claims 25-29 and 31-34 stand rejected under 35 U.S.C. § 112, second paragraph, as being incomplete the Examiner alleging that the claims have omitted essential steps. In particular, the Examiner alleges that the missing steps amount to a gap between the steps, and that the omitted steps comprise a lack of an adequate correlation step.

Although Applicants do not agree with the rejection or comments of the Examiner, Applicants have amended claims 25 and 31 to point out the invention with greater particularity. In particular, claim 25 has been amended to recite "[a] method for identifying a compound that decreases Rheb activity." Further, claim 25 has been amended to conform the remaining steps to correspond to "a reduction in Rheb activity." Still further claim 25 has been amended to recite that "a decrease in the cell size in the first aliquot of cells as compared to the second aliquot of cells is associated with a reduction in Rheb activity" to correlate the final step of the method with the preamble of the claim. In addition, claim 31 has been similarly amended to recite "[a] method for screening a library of candidate compounds to identify a compound that decreases Rheb activity. Further, claim 27 has been cancelled as the limitation of an "antagonist" has been incorporated into amended claim 25. No new matter has been added by the amendments as the specification fully describes the steps of the invention as currently claimed.

Claims 25-29 and 31-34 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner alleges that there is insufficient written description of the Rheb proteins of the claims and that it would require either an adequate description of a common structure and function, or a disclosure of a representative number of Rheb species to support the scope of the claims. The Examiner acknowledges that there is some disclosure of a common function, *e.g.*, the proteins are disclosed as Ras-like, but alleges that there is no discussion of a common structure. Further, the Examiner alleges that the specification discloses just two species of Rheb protein, human or drosophila. In addition, the Examiner asserts that given the distant relationship between humans and drosophila, it is clear that there are at minimum millions of Rheb species and that given these facts, one of skill in the art would conclude that the specification fails to disclosure either a representative number of species, or common functional and structural characteristics, adequately to describe the claimed genus.

Applicants respectfully disagree with the rejection by the Examiner and the reasons set forth in support of those rejections. In particular, the Examiner has asserted that the specification only discloses the Rheb proteins for Drosophila and humans. Applicants respectfully direct the Examiner to the description of Rheb proteins beginning at page 9 and continuing through page 10 (paragraphs 35 through 38) where Rheb proteins from sources other than Drosophila and human are described. In particular, the accession number NP_44305 at page 10, line 2, is a reference to the amino acid sequence for mouse Rheb protein which has been incorporated by reference. Further, it should also be noted that Rheb proteins from rat and other animals were also known in the art prior to the filing date of the present invention. See for example accession number Q62639 (rat Rheb protein, Yamagata *et al.*, *J. Biol. Chem.* 269:16333-16339, 1994). As such, amino acid sequences comprising Rheb proteins from Drosophila, mouse, rat and human, among others were known in the art prior to the filing date of the present invention. Still further, the specification defines certain functions of the Rheb protein. As Rheb proteins are defined in the specification by both amino acid sequence and by functional activity common to all known Rheb proteins the term "Rheb" is fully defined as required by 35 U.S.C. § 112, first paragraph. Therefore, in view of the above remarks Applicants respectfully request the Examiner to reconsider the rejection of claims 25-29 and 31-34.

Rejections Under 35 U.S.C. § 103:

Claims 25 - 29 and 31 - 34 stand rejected under 35 USC 103(a) as being unpatentable over WO 03/016499 in view of Yamagata *et al.* (1994, IDS) and U.S. Patent No. 6,986,993. The Examiner alleges that WO 03/016499 teaches the assay for the identification of lead compounds (including libraries of compounds), for the inhibition of human Ras, said inhibitors being candidates (*e.g.*, lead compounds) for the treatment of cancer (*e.g.*, a disease associated with abnormal cell growth). The reference is noted by the Examiner to differ from the claimed invention in that it does not teach the screening for inhibitors of Rheb nor the screening by the measurement of cell size.

In addition, the Examiner alleges that Yamagata *et al.* teaches that Rheb is a growth factor of the Ras family that is closely related to Ras with the same GTPase activity as Ras. Further, the Examiner alleges that the '993 patent teaches that cell size can be used for the determination of compounds that affect the viability and metastasis of cancer cells.

Based on these allegation the Examiner has concluded that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the method of screening for anti-cancer drugs of WO 03/016499, substituting Rheb for Ras, given the teachings of Yamagata *et al.* that Rheb is a growth factor of the Ras family that is closely related to Ras with the same GTPase activity as Ras. The Examiner alleges that because of the similarities between Ras and Rheb, and Ras being known as a target for anti-cancer treatments, the skilled artisan would have been motivated to screen for Rheb inhibitors as possible anti-cancer drugs as well. The Examiner also alleges that the skilled artisan would have been motivated to employ the method by determining cell size given the teaching of the '933 patent that cell size can be measured for the determination of compounds that affect the viability and metastasis of cancer cells.

Applicants respectfully disagree with the rejection by the Examiner. Yamagata *et al.* disclose that Rheb is a member of the Ras family, but not all members of the Ras family of small GTP-binding proteins have been associated with cancer. In fact, Yamagata *et al.* speculate that because Rheb has a unique structure when compared with other Ras family members, is enriched in brain neurons, and is rapidly regulated by synaptic activity, it may regulate cellular pathways involved in neuronal plasticity. Further, as discussed at paragraphs 6 and 7 of the specification Rheb, unlike Ras, exists in an activated state. In addition, it has been shown that stable transfection of Rheb into mammalian cells does not result in accelerated growth rates or transformation. Further, Rheb has amino acid substitutions found at amino acid positions 15 and 16 that correspond to those positions (positions 12 and 13) found mutated in Ras proteins associated with a transformed phenotype. See Yamagata *et al.* page 16337, right column, lines 8-21). Rheb does not have the same activity as Ras and extrapolation of the

activity of Ras and certain other Ras family members to Rheb is not appropriate. The skilled artisan has no scientific basis for reaching the conclusions alleged by the Examiner.

WO 03/016499 discloses methods of screening for anti-cancer drugs by looking for inhibitors of proliferation and inducing cell death in a population of cancer cells by i) increasing the amount of the differentiation associated with the protein MDA-7, and ii) decreasing RAS activity within the cell population. There is nothing in WO 03/016499 to disclose or suggest that all proteins of the Ras family share the same activity. Further, there is no disclosure directed to the activities of Rheb. As such, WO 03/016499 provides no basis for the artisan of ordinary skill to screen for any agent that reduces the activity of Rheb to be treat a disease associated with cell growth. WO 03/016499 when considered alone or in any combination does not render the methods of the present invention obvious.

US 6,986,993 discloses a system for cell-based screening. There is nothing in the '993 patent to disclose or suggest that Rheb shares any activity with another member of the Ras family. Again, as with WO 03/016499, the '993 patent provides no basis for the artisan of ordinary skill to screen using a cell-based screening system for an agent that reduces the activity of Rheb for any reason. While any number of methods and systems may have been available in the art to measure the size of a cell, without some disclosure that suggests that Rheb shares activity with Ras beyond the ability to bind GTP, there is no basis in the '993 patent either alone or in combination with Yamagata *et al.* and/or WO 03/01699 to obtain the present invention.

In view of the remarks above, Applicants respectfully request the Examiner withdraw the rejection of claims 25 - 29 and 31 - 34 35 USC 103(a) as being unpatentable over WO 03/016499 in view of Yamagata *et al.* (1994) and U.S. Patent No. 6,986,993.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 6 December 2007 By: Brian W. Poor

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